

**ANNEX I**

**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

Targretin 75 mg soft capsules

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 75 mg of bexarotene.

Excipient(s) with known effect: sorbitol

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Soft capsule.

Off-white capsule, containing a liquid suspension and imprinted with “Targretin”.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Targretin is indicated for the treatment of skin manifestations of advanced stage cutaneous T-cell lymphoma (CTCL) in adult patients refractory to at least one systemic treatment.

### 4.2 Posology and method of administration

Bexarotene therapy should only be initiated and maintained by physicians experienced in the treatment of patients with CTCL.

#### Posology

The recommended initial dose is 300 mg/m<sup>2</sup>/day. Initial dose calculations according to body surface area are as follows:

**Table 1 Recommended initial dose**

Initial dose level (300 mg/m <sup>2</sup> /day)		Number of 75 mg Targretin capsules
Body Surface Area (m <sup>2</sup> )	Total daily dose (mg/day)	
0.88 – 1.12	300	4
1.13 - 1.37	375	5
1.38 - 1.62	450	6
1.63 - 1.87	525	7
1.88 - 2.12	600	8
2.13 - 2.37	675	9
2.38 - 2.62	750	10

#### *Dose modification guidelines*

The 300 mg/m<sup>2</sup>/day dose level may be adjusted to 200 mg/m<sup>2</sup>/day then to 100 mg/m<sup>2</sup>/day, or temporarily suspended, if necessitated by toxicity. When toxicity is controlled, doses may be carefully readjusted upward. With appropriate clinical monitoring, individual patients may benefit from doses above 300 mg/m<sup>2</sup>/day. Doses greater than 650 mg/m<sup>2</sup>/day have not been evaluated in patients with CTCL. In clinical trials, bexarotene was administered for up to 118 weeks to patients with CTCL. Treatment should be continued as long as the patient is deriving benefit.

#### *Paediatric population*

The safety and efficacy of bexarotene in children (aged below 18 years) have not been established. No data are available.

#### *Elderly patients*

Of the total number of patients with CTCL in clinical studies, 61% were 60 years or older, while 30% were 70 years or older. No overall differences in safety were observed between patients 70 years or older and younger patients, but greater sensitivity of some older individuals to bexarotene cannot be ruled out. The standard dose should be used in the elderly.

#### *Patients with renal impairment*

No formal studies have been conducted in patients with renal insufficiency. Clinical pharmacokinetic data indicate that urinary elimination of bexarotene and its metabolites is a minor excretory pathway for bexarotene. In all evaluated patients, the estimated renal clearance of bexarotene was less than 1 ml/minute. In view of the limited data, patients with renal insufficiency should be monitored carefully while on bexarotene therapy.

#### Method of administration

For oral use.

Targretin capsules should be taken as a single oral daily dose with a meal. The capsule should not be chewed.

### **4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Pregnancy and lactation.

Women of child-bearing potential without effective birth-control measures.

History of pancreatitis.

Uncontrolled hypercholesterolaemia.

Uncontrolled hypertriglyceridaemia.

Hypervitaminosis A.

Uncontrolled thyroid disease.

Hepatic insufficiency.

Ongoing systemic infection.

### **4.4 Special warnings and precautions for use**

#### *General*

Targretin capsules should be used with caution in patients with a known hypersensitivity to retinoids. No clinical instances of cross-reactivity have been noted. Patients receiving bexarotene should not donate blood for transfusion. Butylated hydroxyanisole, an ingredient in Targretin, may cause irritation to the mucous membranes, therefore the capsules must be swallowed intact and not chewed.

#### *Lipids*

Hyperlipidaemia has been identified as an effect associated with the use of bexarotene in clinical studies. Fasting blood lipid determinations (triglycerides and cholesterol) should be performed before bexarotene therapy is initiated and at weekly intervals until the lipid response to bexarotene is established, which usually occurs within two to four weeks, and then at intervals no less than monthly thereafter. Fasting triglycerides should be normal or normalised with appropriate intervention prior to bexarotene therapy. Every attempt should be made to maintain triglyceride levels below 4.52 mmol/l in order to reduce the risk of clinical sequelae. If fasting triglycerides are elevated or become elevated during treatment, institution of antilipemic therapy is recommended, and if necessary, dose reductions (from 300 mg/m<sup>2</sup>/day of bexarotene to 200 mg/m<sup>2</sup>/day, and if necessary to 100 mg/m<sup>2</sup>/day) or treatment discontinuation. Data from clinical studies indicate that bexarotene concentrations were not affected by concomitant administration of atorvastatin. However, concomitant administration of

gemfibrozil resulted in substantial increases in plasma concentrations of bexarotene and therefore, concomitant administration of gemfibrozil with bexarotene is not recommended (see section 4.5). Elevations of serum cholesterol should be managed according to current medical practice.

#### *Pancreatitis*

Acute pancreatitis associated with elevations of fasting serum triglycerides has been reported in clinical studies. Patients with CTCL having risk factors for pancreatitis (e.g., prior episodes of pancreatitis, uncontrolled hyperlipidaemia, excessive alcohol consumption, uncontrolled diabetes mellitus, biliary tract disease, and medications known to increase triglyceride levels or to be associated with pancreatic toxicity) should not be treated with bexarotene, unless the potential benefit outweighs the risk.

#### *Liver Function Test (LFT) abnormalities*

LFT elevations associated with the use of bexarotene have been reported. Based on data from ongoing clinical trials, elevation of LFTs resolved within one month in 80% of patients following a decrease in dose or discontinuation of therapy. Baseline LFTs should be obtained, and LFTs should be carefully monitored weekly during the first month and then monthly thereafter. Consideration should be given to a suspension or discontinuation of bexarotene if test results reach greater than three times the upper limit of normal values for SGOT/AST, SGPT/ALT, or bilirubin.

#### *Thyroid function test alterations*

Changes in thyroid function tests have been observed in patients receiving bexarotene, most often noted as a reversible reduction in thyroid hormone (total thyroxine [total T<sub>4</sub>]) and thyroid-stimulating hormone (TSH) levels. Baseline thyroid function tests should be obtained and then monitored at least monthly during treatment and as indicated by the emergence of symptoms consistent with hypothyroidism. Patients with symptomatic hypothyroidism on bexarotene therapy have been treated with thyroid hormone supplements with resolution of symptoms.

#### *Leucopenia*

Leucopenia associated with bexarotene therapy has been reported in clinical studies. The majority of cases resolved after dose reduction or discontinuation of treatment. Determination of white blood cell count with differential count should be obtained at baseline, weekly during the first month and then monthly thereafter.

#### *Anaemia*

Anaemia associated with bexarotene therapy has been reported in clinical studies. Determination of haemoglobin should be obtained at baseline, weekly during the first month and then monthly thereafter. Decreases of haemoglobin should be managed according to current medical practice.

#### *Psychiatric disorders*

Depression, depression aggravated, anxiety, and mood alterations have been reported in patients treated with systemic retinoids, including bexarotene. Particular care should be taken in patients with a history of depression. Patients should be monitored for signs of depression and referred for appropriate treatment if necessary. Awareness by family or friends may be useful to detect mental health deterioration.

#### *Lens opacities*

Following bexarotene treatment, some patients were observed to have previously undetected lens opacities or a change in pre-existing lens opacities unrelated to treatment duration or dose level of exposure. Given the high prevalence and natural rate of cataract formation in the older patient population represented in the clinical studies, there was no apparent association between the incidence of lens opacity formation and bexarotene administration. However, an adverse effect of long-term bexarotene treatment on lens opacity formation in humans has not been excluded. Any patient treated with bexarotene who experiences visual difficulties should have an appropriate ophthalmologic examination.

#### *Vitamin A supplementation*

Because of the relationship of bexarotene to vitamin A, patients should be advised to limit vitamin A supplements to  $\leq 15,000$  IU/day to avoid potential additive toxic effects.

#### *Patients with diabetes mellitus*

Caution should be exercised when administering bexarotene in patients using insulin, agents enhancing insulin secretion (e.g. sulfonylureas), or insulin-sensitisers (e.g. thiazolidinediones). Based on the known mechanism of action, bexarotene may potentially enhance the action of these agents, resulting in hypoglycaemia. No cases of hypoglycaemia associated with the use of bexarotene as monotherapy have been reported.

#### *Photosensitivity*

The use of some retinoids has been associated with photosensitivity. Patients should be advised to minimise exposure to sunlight and avoid sun lamps during therapy with bexarotene, as *in vitro* data indicate that bexarotene may potentially have a photosensitising effect.

#### *Oral contraceptives*

Bexarotene can potentially induce metabolic enzymes and thereby theoretically reduce the efficacy of oestrogenic contraceptives. Thus, if treatment with bexarotene is intended in a woman of childbearing potential, a reliable, non-hormonal form of contraception is also required, because bexarotene belongs to a therapeutic class for which the human malformative risk is high.

#### Paediatric population

Targretin is not recommended in children (aged below 18 years).

Targretin contains a small amount of sorbitol, therefore patients with rare hereditary problems of fructose intolerance should not take this medicine.

### **4.5 Interaction with other medicinal products and other forms of interaction**

#### *Effects of other substances on bexarotene*

No formal studies to evaluate interactions with bexarotene have been conducted. On the basis of the oxidative metabolism of bexarotene by cytochrome P450 3A4 (CYP3A4), coadministration with other CYP3A4 substrates such as ketoconazole, itraconazole, protease inhibitors, clarithromycin and erythromycin may theoretically lead to an increase in plasma bexarotene concentrations. Furthermore, co-administration with CYP3A4 inducers such as rifampicin, phenytoin, dexamethasone or phenobarbital may theoretically cause a reduction in plasma bexarotene concentrations.

Caution is advised in case of combination with CYP3A4 substrates having a narrow therapeutic margin i.e. immunosuppressive agents (cyclosporine, tacrolimus, sirolimus) as well as CYP3A4-metabolised cytotoxics, i.e. cyclophosphamide, etoposide, finasteride, ifosfamide, tamoxifen, vinca-alkaloids.

A population analysis of plasma bexarotene concentrations in patients with CTCL indicated that concomitant administration of gemfibrozil resulted in substantial increases in plasma concentrations of bexarotene. The mechanism of this interaction is unknown. Under similar conditions, bexarotene concentrations were not affected by concomitant administration of atorvastatin or levothyroxine. Concomitant administration of gemfibrozil with bexarotene is not recommended.

#### *Effects of bexarotene on other substances*

There are indications that bexarotene may induce CYP3A4. Therefore, repeated administration of bexarotene may result in an auto-induction of its own metabolism and, particularly at dose levels greater than  $300 \text{ mg/m}^2/\text{day}$ , may increase the rate of metabolism and reduce plasma concentrations of other substances metabolised by cytochrome P450 3A4, such as tamoxifen. For example bexarotene may reduce the efficacy of oral contraceptives (see sections 4.4 and 4.6).

Bexarotene may potentially enhance the action of insulin, agents enhancing insulin secretion (e.g. sulfonylureas), or insulin-sensitisers (e.g. thiazolidinediones), resulting in hypoglycaemia (see section 4.4).

#### *Laboratory test interactions*

CA125 assay values in patients with ovarian cancer may be accentuated with bexarotene therapy.

#### *Food interactions*

In all clinical trials, patients were instructed to take Targretin capsules with or immediately following a meal. In one clinical study, plasma bexarotene AUC and  $C_{\max}$  values were substantially higher following the administration of a fat-containing meal versus those following the administration of a glucose solution. Because safety and efficacy data from clinical trials are based upon administration with food, it is recommended that Targretin capsules be administered with food.

On the basis of the oxidative metabolism of bexarotene by cytochrome P450 3A4, grapefruit juice may theoretically lead to an increase in plasma bexarotene concentrations.

### **4.6 Fertility, pregnancy and lactation**

#### Pregnancy

There are no adequate data from the use of bexarotene in pregnant women. Studies in animals have shown reproductive toxicity. Based on the comparison of animal and patient exposures to bexarotene, a margin of safety for human teratogenicity has not been demonstrated (see section 5.3). Bexarotene is contraindicated in pregnancy (see section 4.3).

If this medicinal product is used inadvertently during pregnancy, or if the patient becomes pregnant while taking this medicinal product, the patient should be informed of the potential hazard to the foetus.

#### Contraception in males and females

Women of childbearing potential must use adequate birth-control measures when bexarotene is used. A negative, sensitive, pregnancy test (e.g. serum beta-human chorionic gonadotropin, beta-HCG) should be obtained within one week prior to bexarotene therapy. Effective contraception must be used from the time of the negative pregnancy test through the initiation of therapy, during therapy and for at least one month following discontinuation of therapy. Whenever contraception is required, it is recommended that two reliable forms of contraception be used simultaneously. Bexarotene can potentially induce metabolic enzymes and thereby theoretically reduce the efficacy of oestroprogestative contraceptives (see section 4.5). Thus, if treatment with bexarotene is intended in a woman with childbearing potential, a reliable, non-hormonal contraceptive method is also recommended. Male patients with sexual partners who are pregnant, possibly pregnant, or may potentially become pregnant must use condoms during sexual intercourse while taking bexarotene and for at least one month after the last dose.

#### Breast-feeding

It is unknown whether bexarotene is excreted in human milk. Bexarotene should not be used in breast-feeding mothers.

#### Fertility

There are no human data on the effect of bexarotene on fertility. In male dogs, some effects have been documented (see section 5.3). Effects on fertility cannot be excluded.

### **4.7 Effects on ability to drive and use machines**

No studies on the effects on the ability to drive and use machines have been performed. However, dizziness and visual difficulties have been reported in patients taking Targretin. Patients who experience dizziness or visual difficulties during therapy must not drive or operate machinery.

## 4.8 Undesirable effects

### Summary of the safety profile

The safety of bexarotene has been examined in clinical studies of 193 patients with CTCL who received bexarotene for up to 118 weeks and in 420 non-CTCL cancer patients in other studies.

In 109 patients with CTCL treated at the recommended initial dose of 300 mg/m<sup>2</sup>/day, the most commonly reported adverse reactions to Targretin were hyperlipaemia ((primarily elevated triglycerides) 74%), hypothyroidism (29%), hypercholesterolaemia (28%), headache (27%), leucopenia (20%), pruritus (20%), asthenia (19%), rash (16%), exfoliative dermatitis (15%), and pain (12%).

### Tabulated list of adverse reactions

The following Targretin-related adverse reactions were reported during clinical studies in patients with CTCL (N=109) treated at the recommended initial dose of 300 mg/m<sup>2</sup>/day. The frequencies of adverse reactions are classified as very common (>1/10), common (>1/100, <1/10), uncommon (>1/1,000, <1/100), rare (>1/10,000, <1/1,000), and very rare (<1/10,000).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

**Table 2 Adverse reactions reported in patients in clinical trials**

<b>System Organ Class (MedDRA terminology*)</b>	<b>Very Common</b>	<b>Common</b>	<b>Uncommon</b>
<b>Blood and lymphatic system disorders</b>	Leucopenia	Lymphoma Like Reaction Lymphadenopathy Hypochromic Anaemia <sup>1,2,3</sup>	Blood Dyscrasia Purpura Coagulation Disorder Coagulation Time Increased <sup>2,3</sup> Anaemia <sup>1</sup> Thrombocytopenia <sup>3</sup> Thrombocythemia Eosinophilia <sup>1</sup> Leukocytosis <sup>2</sup> Lymphocytosis
<b>Endocrine disorders</b>	Hypothyroidism	Thyroid Disorder	Hyperthyroidism
<b>Metabolism and nutrition disorders</b>	Hyperlipaemia Hypercholesterolaemia	Weight Gain SGOT Increased SGPT Increased Lactic Dehydrogenase Increased Creatinine Increased Hypoproteinaemia	Gout Bilirubinemia <sup>1,3</sup> BUN Increased <sup>1</sup> High Density Lipoprotein Decreased
<b>Nervous system disorders</b>		Dizziness Hypesthesia Insomnia	Ataxia Neuropathy Vertigo Hyperaesthesia Depression <sup>1,2,3</sup> Agitation
<b>Eye disorders</b>		Dry Eyes Eye Disorder	Cataract Specified <sup>1,2,3</sup> Amblyopia <sup>3</sup> Visual Field Defect Corneal Lesion Abnormal Vision <sup>1,2,3</sup> Blepharitis Conjunctivitis <sup>3</sup>

<b>System Organ Class</b> (MedDRA terminology*)	<b>Very Common</b>	<b>Common</b>	<b>Uncommon</b>
<b>Ear and labyrinth disorders</b>		Deafness	Ear disorder
<b>Cardiac disorders</b>			Tachycardia
<b>Vascular disorders</b>		Peripheral Oedema	Haemorrhage Hypertension Oedema <sup>3</sup> Vasodilatation <sup>1,2,3</sup> Varicose Vein
<b>Gastrointestinal disorders</b>		Vomiting Diarrhoea <sup>1,3</sup> Nausea <sup>3</sup> Anorexia <sup>1</sup> Liver Function Tests Abnormal Cheilitis <sup>2</sup> Dry Mouth <sup>2,3</sup> Constipation Flatulence	Pancreatitis <sup>1,3</sup> Hepatic Failure Gastrointestinal Disorder <sup>1</sup>
<b>Skin and subcutaneous tissue disorders</b>	Exfoliative Dermatitis Pruritus Rash	Skin Ulcer Alopecia <sup>1</sup> Skin Hypertrophy Skin Nodule Acne Sweating Dry Skin <sup>2,3</sup> Skin Disorder	Serous Drainage <sup>1</sup> Herpes Simplex Pustular Rash Skin Discoloration <sup>3</sup> Hair Disorder <sup>1</sup> Nail Disorder <sup>1,3</sup>
<b>Musculoskeletal and connective tissue disorders</b>		Bone Pain Arthralgia Myalgia	Myasthenia <sup>1</sup>
<b>Renal and urinary disorders</b>			Albuminuria <sup>1,3</sup> Kidney Function Abnormal
<b>General disorders and administration site conditions</b>	Pain Headache Asthma	Allergic Reaction Infection Chills <sup>1</sup> Abdominal Pain Hormone Level Altered <sup>1</sup>	Neoplasm Fever <sup>1,2,3</sup> Cellulitis Infection Parasitic Mucous Membrane Disorder <sup>3</sup> Back Pain <sup>1,2,3</sup> Lab Test Abnormal

- 1: adverse reactions noted with increased frequency when bexarotene was administered at a dose >300mg/m<sup>2</sup>/day.
- 2: adverse reactions noted with increased frequency when bexarotene was administered at a dose of 300 mg/m<sup>2</sup>/day in non-CTCL cancer patients.
- 3: adverse reactions noted with increased frequency when bexarotene was administered at a dose of >300 mg/m<sup>2</sup>/day (compared to administration to CTCL patients at 300 mg/m<sup>2</sup>/day) in non-CTCL cancer patients.

**Additional adverse reactions observed when used outside of the recommended dose and indication (i.e. used in CTCL at an initial dose >300mg/m<sup>2</sup>/day or in non-CTCL cancer indications):**



#### Newly observed adverse reactions

Ecchymosis, petechia, abnormal white blood cells, thromboplastin decreased, abnormal erythrocytes, dehydration, increased gonadotrophic luteinizing hormone, weight loss, increased alkaline phosphatase, increased creatinine phosphokinase, lipase increased, hypercalcaemia, migraine, peripheral neuritis, paraesthesia, hypertonia, confusion, anxiety, emotional lability, somnolence, decreased libido, nervousness, night blindness, nystagmus, lacrimation disorder, tinnitus, taste perversion, chest pain, arrhythmia, peripheral vascular disorder, generalized oedema, haemoptysis, dyspnoea, increased cough, sinusitis, pharyngitis, dysphagia, mouth ulceration, oral moniliasis, stomatitis, dyspepsia, thirst, abnormal stools, eructation, vesicobullous rash, maculopapular rash, leg cramps, haematuria, flu syndrome, pelvic pain, and body odour.

Single observations of the following were also reported: bone marrow depression, decreased prothrombin, decreased gonadotrophic luteinizing hormone, increased amylase, hyponatraemia, hypokalaemia, hyperuricaemia, hypocholesterolaemia, hypolipidaemia, hypomagnesaemia, abnormal gait, stupor, circumoral paraesthesia, abnormal thinking, eye pain, hypovolaemia, subdural haematoma, congestive heart failure, palpitation, epistaxis, vascular anomaly, vascular disorder, pallor, pneumonia, respiratory disorder, lung disorder, pleural disorder, cholecystitis, liver damage, jaundice, cholestatic jaundice, melaena, vomiting, laryngismus, tenesmus, rhinitis, increased appetite, gingivitis, herpes zoster, psoriasis, furunculosis, contact dermatitis, seborrhoea, lichenoid dermatitis, arthritis, joint disorder, urinary retention, impaired urination, polyuria, nocturia, impotence, urine abnormality, breast enlargement, carcinoma, photosensitivity reaction, face oedema, malaise, viral infection, enlarged abdomen.

The majority of adverse reactions were noted at a higher incidence at doses greater than 300 mg/m<sup>2</sup>/day. Generally, these resolved without sequelae on dose reduction or withdrawal of treatment. However, among a total of 810 patients, including those without malignancy, treated with bexarotene, there were three serious adverse reactions with fatal outcome (acute pancreatitis, subdural haematoma and liver failure). Of these, liver failure, subsequently determined to be not related to bexarotene, was the only one to occur in a CTCL patient.

Hypothyroidism generally occurs 4-8 weeks after commencement of therapy. It may be asymptomatic and responds to treatment with thyroxine and resolves upon withdrawal of treatment.

Bexarotene has a different adverse reaction profile to other oral, non-retinoid X receptor (RXR)-selective retinoids. Owing to its primarily RXR-binding activity, bexarotene is less likely to cause mucocutaneous, nail, and hair toxicities; arthralgia; and myalgia; which are frequently reported with retinoic acid receptor (RAR) -binding agents.

#### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

## **4.9 Overdose**

No clinical experience with an overdose of Targretin has been reported. Any overdose should be treated with supportive care for the signs and symptoms exhibited by the patient.

Doses up to 1000 mg/m<sup>2</sup>/day of bexarotene have been administered in clinical studies with no acute toxic effects. Single doses of 1500 mg/kg (9000 mg/m<sup>2</sup>) and 720 mg/kg (14,400 mg/m<sup>2</sup>) were tolerated without significant toxicity in rats and dogs, respectively.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other antineoplastic agents, ATC code: L01XX25

#### Mechanism of action

Bexarotene is a synthetic compound that exerts its biological action through selective binding and activation of the three RXRs:  $\alpha$ ,  $\beta$ , and  $\gamma$ . Once activated, these receptors function as transcription factors that regulate processes such as cellular differentiation and proliferation, apoptosis, and insulin sensitisation. The ability of the RXRs to form heterodimers with various receptor partners that are important in cellular function and in physiology indicates that the biological activities of bexarotene are more diverse than those of compounds that activate the RARs.

*In vitro*, bexarotene inhibits the growth of tumour cell lines of haematopoietic and squamous cell origin. *In vivo*, bexarotene causes tumour regression in some animal models and prevents tumour induction in others. However, the exact mechanism of action of bexarotene in the treatment of cutaneous T-cell lymphoma (CTCL) is unknown.

#### Clinical results

Bexarotene capsules were evaluated in clinical trials of 193 patients with CTCL of whom 93 had advanced stage disease refractory to prior systemic therapy. Among the 61 patients treated at an initial dose of 300 mg/m<sup>2</sup>/day, the overall response rate, according to a global assessment by the physician, was 51% (31/61) with a clinical complete response rate of 3%. Responses were also determined by a composite score of five clinical signs (surface area, erythema, plaque elevation, scaling and hypo/hyperpigmentation) which also considered all extracutaneous CTCL manifestations. The overall response rate according to this composite assessment was 31% (19/61) with a clinical complete response rate of 7% (4/61).

### 5.2 Pharmacokinetic properties

#### Absorption

*Absorption/dose proportionality*: pharmacokinetics were linear up to a dose of 650 mg/m<sup>2</sup>. Terminal elimination half-life values were generally between one and three hours. Following repeat once daily dose administration at dose levels  $\geq 230$  mg/m<sup>2</sup>,  $C_{\max}$  and AUC in some patients were less than respective single dose values. No evidence of prolonged accumulation was observed. At the recommended initial daily-dose level (300 mg/m<sup>2</sup>), single-dose and repeated daily-dose bexarotene pharmacokinetic parameters were similar.

#### Distribution

*Protein binding/distribution*: bexarotene is highly bound (>99%) to plasma proteins. The uptake of bexarotene by organs or tissues has not been evaluated.

#### Biotransformation

*Metabolism*: bexarotene metabolites in plasma include 6- and 7-hydroxy-bexarotene and 6- and 7-oxo-bexarotene. *In vitro* studies suggest glucuronidation as a metabolic pathway, and that cytochrome P450 3A4 is the major cytochrome P450 isozyme responsible for formation of the oxidative metabolites. Based on the *in vitro* binding and the retinoid receptor activation profile of the metabolites, and on the relative amounts of individual metabolites in plasma, the metabolites have little impact on the pharmacological profile of retinoid receptor activation by bexarotene.

## Elimination

*Excretion:* neither bexarotene nor its metabolites are excreted in urine in any appreciable amounts. The estimated renal clearance of bexarotene is less than 1 ml/minute. Renal excretion is not a significant elimination pathway for bexarotene.

### *Pharmacokinetics in Special Populations*

*Age:* Based on the population pharmacokinetic analysis of data for 232 patients aged  $\geq 65$  years and 343 patients aged  $< 65$  years, age has no statistically significant effect on bexarotene pharmacokinetics.

*Body Weight and Gender:* Based on the population pharmacokinetics analysis of data for 614 patients with a weight range of 26 to 145 kg, the bexarotene apparent clearance increases with increasing body weight. Gender has no statistically significant effect on bexarotene pharmacokinetics.

*Race:* Based on the population pharmacokinetic analysis of data for 540 Caucasian and 44 Black patients, bexarotene pharmacokinetics are similar in Blacks and Caucasians. There are insufficient data to evaluate potential differences in the pharmacokinetics of bexarotene for other races.

## **5.3 Preclinical safety data**

Bexarotene is not genotoxic. Carcinogenicity studies have not been conducted. Fertility studies have not been conducted; however, in sexually immature male dogs, reversible aspermatogenesis (28-day study) and testicular degeneration (91-day study) were seen. When bexarotene was administered for six months to sexually mature dogs, no testicular effects were seen. Effects on fertility cannot be excluded. Bexarotene, in common with the majority of retinoids, was teratogenic and embryotoxic in an animal test species at systemic exposures that are achievable clinically in humans. Irreversible cataracts involving the posterior area of the lens occurred in rats and dogs treated with bexarotene at systemic exposures that are achievable clinically in humans. The aetiology of this finding is unknown. An adverse effect of long-term bexarotene treatment on cataract formation in humans has not been excluded.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

#### Capsule content:

macrogol  
polysorbate  
povidone  
butylated hydroxyanisole

#### Capsule shell:

gelatin  
sorbitol special-glycerin blend (glycerin, sorbitol, sorbitol anhydrides (1,4-sorbitan), mannitol and water)  
titanium dioxide (E171)  
printing ink (SDA 35A alcohol (ethanol & ethyl acetate), propylene glycol (E1520), iron oxide black (E172), polyvinyl acetate phthalate, purified water, isopropyl alcohol, macrogol 400, ammonium hydroxide 28%)

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

3 years

### **6.4 Special precautions for storage**

Do not store above 30°C.

Keep the bottle tightly closed.

### **6.5 Nature and contents of container**

High-density polyethylene bottles with child-resistant closures containing 100 capsules.

### **6.6 Special precautions for disposal and other handling**

No special requirements for disposal.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## **7. MARKETING AUTHORISATION HOLDER**

Eisai Ltd.  
European Knowledge Centre  
Mosquito Way  
Hatfield  
Hertfordshire  
AL10 9SN  
United Kingdom  
tel: +44 (0)208 600 1400  
fax: +44 (0)208 600 1401  
e-mail: EUmedinfo@eisai.net

## **8. MARKETING AUTHORISATION NUMBER**

EU/1/01/178/001

## **9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 29 March 2001.

Date of latest renewal: 29 March 2006.

## **10. DATE OF REVISION OF THE TEXT**

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

## **ANNEX II**

- A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

**A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**

Name and address of the manufacturer responsible for batch release

Eisai Manufacturing Limited  
European Knowledge Centre  
Mosquito Way  
Hatfield  
Hertfordshire  
AL10 9SN  
United Kingdom

**B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

**C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) ) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

**D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

- **Risk Management Plan (RMP)**

Not applicable.

**ANNEX III**  
**LABELLING AND PACKAGE LEAFLET**

## **A. LABELLING**



**PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING**

**OUTER CARTON TEXT AND BOTTLE LABEL TEXT**

**1. NAME OF THE MEDICINAL PRODUCT**

Targretin 75 mg soft capsules  
Bexarotene

**2. STATEMENT OF ACTIVE SUBSTANCE**

One capsule contains 75 mg of bexarotene.

**3. LIST OF EXCIPIENTS**

Contains sorbitol. See leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

100 soft capsules

**5. METHOD AND ROUTE OF ADMINISTRATION**

Oral use.  
To be swallowed whole.  
Read the package leaflet before use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

Do not store above 30°C.  
Keep the bottle tightly closed.

<b>10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE</b>
--

<b>11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER</b>
---

Eisai Ltd.  
Mosquito Way  
Hatfield  
Hertfordshire  
AL10 9SN  
United Kingdom

<b>12. MARKETING AUTHORISATION NUMBER(S)</b>
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EU/1/01/178/001

<b>13. BATCH NUMBER</b>
-------------------------

Batch

<b>14. GENERAL CLASSIFICATION FOR SUPPLY</b>
--

Medicinal product subject to medical prescription.

<b>15. INSTRUCTIONS ON USE</b>
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<b>16. INFORMATION IN BRAILLE</b>
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Targretin 75 mg

<b>17. UNIQUE IDENTIFIER – 2D BARCODE</b>
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2D barcode carrying the unique identifier included.

<b>18. UNIQUE IDENTIFIER - HUMAN READABLE DATA</b>
--

PC:  
SN:  
NN:

## **B. PACKAGE LEAFLET**

## **Package leaflet: Information for the user**

### **TARGRETIN 75 mg soft capsules Bexarotene**

**Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

#### **What is in this leaflet**

1. What Targretin is and what it is used for
2. What you need to know before you take Targretin
3. How to take Targretin
4. Possible side effects
5. How to store Targretin
6. Contents of the pack and other information

#### **1. What Targretin is and what it is used for**

The active substance in Targretin, bexarotene, belongs to a group of medicines known as retinoids, which are related to vitamin A.

Targretin capsules are used by patients with advanced stage cutaneous T-cell lymphoma (CTCL) whose disease has not responded to other therapies. CTCL is a condition in which certain cells of the body's lymph system called T-lymphocytes become cancerous and affect the skin.

#### **2. What you need to know before you take Targretin**

##### **Do not take Targretin:**

- if you are allergic to bexarotene or any of the other ingredients of this medicine (listed in section 6).
- if you are pregnant or breast feeding or if you can become pregnant and are not using effective birth control measures.
- if you have a history of pancreatitis, have uncontrolled lipid (blood fats) elevations (high blood cholesterol or high blood triglycerides), have a condition known as hypervitaminosis A, have uncontrolled thyroid disease, have insufficient liver function or have an ongoing systemic infection.

##### **Warnings and precautions**

Talk to your doctor before taking Targretin

- if you have a known hypersensitivity to retinoids (related to vitamin A), suffer from liver disease, have high blood lipids or take medicines which may cause high blood lipids, have uncontrolled diabetes mellitus (sugar diabetes), have had gall bladder or biliary tract disease, or consume excessive amounts of alcohol.
- if you have ever had any mental health problems including depression, aggressive tendencies or mood changes. This is because taking Targretin may affect your mood.

Your fasting blood lipid determinations may have to be performed before therapy is initiated and at weekly intervals afterwards, and then monthly while taking this medicine.

Blood tests to evaluate the function of your liver and thyroid gland and to monitor your red blood cell and white blood cell counts will be obtained before therapy is started and will be monitored during therapy.

Periodic eye exams may be needed if you experience visual difficulties while taking this medicine.

Minimise exposure to sunlight as much as possible and avoid exposure to sun lamps.

Do not take more than 15,000 International Units of vitamin A supplements per day during treatment.

#### **Mental health problems**

You may not notice some changes in your mood and behaviour and so it is very important that you tell your friends and family that this medicine could affect your mood and behaviour. They may notice these changes and help you identify any problems that you need to talk to your doctor about.

#### **Children and adolescents**

Targretin capsules should not be used in children or adolescents.

#### **Other medicines and Targretin**

Tell your doctor if you are taking, have recently taken or might take any other medicines, such as

- ketoconazole and itraconazole (used against fungal infections),
- erythromycin, clarithromycin and rifampicin (used against bacterial infections),
- phenytoin and phenobarbital (used against seizures),
- gemfibrozil (used to reduce high levels of fats in the blood such as triglycerides and cholesterol),
- vitamin A supplements, protease inhibitors (used against viral infections),
- tamoxifen (used against some forms of cancer),
- dexamethasone (used for inflammatory conditions),
- insulin, agents enhancing insulin secretion, or insulin-sensitisers (used against diabetes mellitus).

This is important as using more than one medicine at the same time can strengthen or weaken the effect of the medicines.

#### **Targretin with food and drink**

Targretin should be taken with food (see section 3). If you regularly consume grapefruit or grapefruit juice, please consult your doctor as these have the potential to alter your body's response to Targretin therapy.

#### **Pregnancy and breast-feeding**

Targretin may be harmful to a developing foetus. **DO NOT** use Targretin if you are pregnant or breast-feeding. If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

If you are capable of becoming pregnant, you must have a pregnancy test within one week before you start therapy, confirming you are not pregnant. You must use effective contraception (birth control) continuously starting one month before beginning therapy until one month after you stop taking Targretin. It is recommended that two reliable forms of contraception be used together. If you are taking a hormonal contraceptive (for example, birth control pills), you should discuss this with your doctor.

If you are male and your partner is pregnant or capable of becoming pregnant, you must use condoms during sexual intercourse while taking bexarotene and for at least one month after the last dose.

**Driving and using machines**

It is not known whether Targretin has an effect on your ability to drive a car or operate machinery. If you experience dizziness or problems with your vision during therapy, do not drive or operate machinery.

**Targretin contains sorbitol and butylated hydroxyanisole**

Targretin contains a small amount of sorbitol (a type of sugar). If you have an intolerance to some sugars, speak to your doctor before taking this medicinal product.

Butylated hydroxyanisole may cause irritation to the mucous membranes, therefore the capsules must be swallowed intact and not chewed.

**3. How to take Targretin**

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

The doctor will prescribe a suitable dose for you.

The recommended dose is generally 4 to 10 capsules to be taken once daily. Take your prescribed number of capsules at the same time each day with a meal. The capsules can be taken immediately before, during or immediately after the course of the meal, if preferred. The capsules should be swallowed whole and not chewed.

**How long you should take Targretin**

Although some patients have improvement within the first several weeks, most patients require several months or more of treatment to improve.

**If you take more Targretin than you should**

If you have taken more than the prescribed dose of Targretin, you must contact your doctor.

**If you forget to take Targretin**

If you forget to take one dose, take your daily dose with your next meal on the same day, then take your usual dose as normal, the following day. Do not take a double dose in one day to make up for a forgotten dose the previous day.

**If you stop taking Targretin**

Your doctor should determine how long you should take Targretin, and when treatment may be stopped. Do not stop taking your medication until your doctor advises you to do so.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

**4. Possible side effects**

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor as soon as possible if you feel any deterioration in your condition while you are taking Targretin. Sometimes it is necessary to adjust the dose or interrupt treatment. Your doctor will advise you on what to do.

The following side effects were reported in patients with CTCL who were treated with the recommended initial dose of capsules.

Very common (can occur in more than 1 in 10 patients treated):

Low white blood cell count.

Lowering of thyroid hormones level.

Elevation of blood fats (triglycerides and cholesterol).

Skin reactions (Itching, redness, irritation, peeling).

Headache, fatigue, pain.

Common (can occur in up to 1 in 10 patients treated):

Low red blood cell count, enlarged lymph nodes, worsening of lymphoma.

Thyroid disorder.

Elevation of liver enzymes, impaired kidney function, low protein in blood, weight gain.

Insomnia, dizziness, reduced skin sensation.

Dry eyes, deafness, abnormal sensations of the eye including irritation and heaviness.

Swelling of legs and arms.

Nausea, diarrhoea, dry mouth, dry lips, loss of appetite, constipation, excess gas, abnormal liver function tests, vomiting.

Dry skin, skin disorder, loss of hair, skin ulcer, acne, skin thickening, skin nodule, increased sweating.

Joint aches, bone pain, muscle aches.

Chills, abdominal pain, allergic reaction, infection.

Uncommon (can occur in up to 1 in 100 patients treated):

Blood disorders, eosinophilia, leukocytosis, lymphocytosis, purpura, elevated and decreased numbers of blood platelets.

Overactive thyroid.

Elevated bilirubin in the blood, impaired kidney function, gout, decreased HDL cholesterol.

Agitation, difficulties with balance, depression, increased skin sensation on touching, abnormal nerve sensations, vertigo.

Abnormal vision, blurred vision, inflammation of the eye lids, cataract, inflammation of the white part of the eye, lesion of the cornea of the eye, ear disorder, defect in field of vision.

Swelling, bleeding, high blood pressure, fast heart rate, visible vein enlargement, dilation of blood vessels.

Gastrointestinal disorder, liver failure, inflammation of the pancreas.

Changes in hair, herpes simplex, nail disorder, pustular rash, serous drainage, skin discoloration.

Muscle weakness.

Proteins in urine, abnormal kidney function.

Back pain, skin infection, fever, parasitic infection, abnormal laboratory test, disorder of mucous membrane, tumour.

Rare fatal side effects are acute inflammation of the pancreas, bleeding in the head, and liver failure.

**Reporting of side effects**

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

**5. How to store Targretin**

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label. The expiry date refers to the last day of that month.

Do not store above 30°C. Keep the bottle tightly closed.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

## **6. Contents of the pack and other information**

### **What Targretin contains**

Each Targretin capsule contains 75 mg of the active substance bexarotene.

The capsules also contain the other ingredients macrogol, polysorbate, povidone and butylated hydroxyanisole.

The capsule shell consists of gelatin, sorbitol special-glycerine blend (glycerin, sorbitol, sorbitol anhydrides (1,4-sorbitan), mannitol and water), titanium dioxide (E171) and printing ink (SDA 35A alcohol (ethanol & ethyl acetate), propylene glycol (E1520), iron oxide black (E172), polyvinyl acetate phthalate, purified water, isopropyl alcohol, macrogol 400, ammonium hydroxide 28%).

### **What Targretin looks like and contents of the pack**

Targretin is available as soft capsules for oral use in a white plastic bottle containing 100 capsules.

### **Marketing Authorisation Holder**

Eisai Ltd.  
Mosquito Way  
Hatfield  
Hertfordshire  
AL10 9SN  
United Kingdom  
e-mail: EUmedinfo@eisai.net

### **Manufacturer**

Eisai Manufacturing Limited  
Mosquito Way  
Hatfield  
Hertfordshire  
AL10 9SN  
United Kingdom

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

#### **België/Belgique/Belgien**

Eisai SA/NV  
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#### **Lietuva**

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(Jungtinė Karalystė)

#### **България**

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(Обединено кралство)

#### **Luxembourg/Luxemburg**

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#### **Česká republika**

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#### **Magyarország**

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(Marea Britanie)

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(Ruotsi)

**Sverige**

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**United Kingdom**

Eisai Ltd.  
Tel: +44 (0)208 600 1400

**This leaflet was last revised in**

**Other sources of information**

Detailed information on this medicine is available on the European Medicines Agency web site:  
<http://www.ema.europa.eu>.

## **Annex IV**

### **Scientific conclusions**

## **Scientific conclusions**

On 7 July 2016 the United Kingdom triggered a referral under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data, and requested the PRAC to review the routine risk minimisation measures in place for the oral and topical retinoids to ensure the available data and the risks associated with the adverse teratogenic effects and neuropsychiatric disorders are accurately and consistently addressed within the product information where appropriate and justified by data. Furthermore, the PRAC was requested to review any additional risk minimisation measures to ensure that these are optimal in terms of provision of information and delivery of effective risk management that is subject to appropriate monitoring. The PRAC was requested to assess the impact of the above concerns on the benefit-risk balance of retinoid-containing medicinal products and issue a recommendation on whether the products should be maintained, varied, suspended or revoked.

After reviewing all the available data to address the concerns discussed, the PRAC adopted a recommendation on 8 February 2018 which was then considered by the CHMP, in accordance with Article 107k of Directive 2001/83/EC.

## **Overall summary of the scientific evaluation by the PRAC**

The PRAC reviewed all available data from pre-clinical studies, pharmacovigilance data, published literature and spontaneous reports on the risks associated with the adverse teratogenic effects and neuropsychiatric disorders of oral and topical retinoids. In addition, the views of patients and healthcare professionals regarding communication, awareness and understanding of the risks of retinoids during pregnancy and in women of childbearing potential were taken into account in the recommendation along with their views on options for improving risk communication.

The review confirms the already known teratogenic risks associated with the use of oral retinoids in pregnant women. The data suggest that the risk of adverse pregnancy outcomes is more strongly associated with the oral retinoids than the topical retinoids. The animal reproductive toxicity data for the oral retinoids demonstrate a typical pattern of retinoid embryopathy. The human data on congenital malformations after oral retinoid exposure show a significant risk of retinoid embryopathy (of up to 30% of fetuses exposed); furthermore it is known that approximately one-third of pregnant patients exposed to oral retinoids during pregnancy will have spontaneous abortions. Pregnancy is an absolute contraindication for all oral retinoids in the EU.

The PRAC noted that despite the introduction of pregnancy prevention measures, including pregnancy prevention programmes (PPPs), cases of pregnancy during treatment with oral retinoid continue to be reported in the EU.

Compliance with the PPP is crucial to a positive benefit/risk balance for these products; therefore, the adequacy of the pregnancy prevention measures, including PPPs, for the oral retinoids acitretin, alitretinoin and isotretinoin has been reviewed to ensure that the available materials effectively encourage contraception use, regular pregnancy testing and shared responsibility between patients, doctors and pharmacists in adhering to recommendations, and that this is communicated consistently and effectively for all products. Furthermore, specific studies to measure effectiveness of the agreed changes to the PPP have been imposed on the marketing authorisation holders as an outcome of the referral.

In this respect, the PRAC recommended amendments to the product information, including harmonising the warnings and precautions of use for the oral retinoids acitretin, alitretinoin and isotretinoin to reflect the teratogenic risk associated with their use and communication to healthcare professionals through a direct healthcare professional communication. In addition, the PRAC recommended changes to the educational materials for the oral retinoids (acitretin, alitretinoin and isotretinoin) to ensure healthcare professionals and patients are informed about the risks associated with oral retinoids (acitretin, alitretinoin and isotretinoin) in pregnant women and women of child-

bearing potential and on the measures necessary to minimise the risk. These include a patient reminder card, physician checklist/acknowledgement form and pharmacist checklist ensuring the understanding and the awareness of prescribers and patients on the risks. The PRAC has also recommended that educational materials be distributed via electronic channels such as QR codes, and websites to make better use of the existing technology bearing in mind the young patient population using these products.

The PRAC acknowledged that the implementation of the following elements of the PPP need to be considered and agreed at national level to account for the different healthcare systems in the EU:

- The implementation of the 7-day prescription validity rule, in order not to impact on existing national legislation where 7 days validity exists;
- Patient signature of the physician checklist/acknowledgement form;
- Dissemination of the patient reminder card;
- Pharmacist checklist;
- Inclusion of appointment table in the patient reminder card;
- The option of a pictogram/symbol to accompany the box warning wording and to be included in the visual reminder on the outer package to warn patients about the harm to unborn baby and the need for effective contraception when using the medicinal product.

PRAC considered that given the oncological indications of oral tretinoin and oral bexarotene, further risk minimisation measures (RMMs) for these products regarding teratogenic effects, such as strengthening the product information (PI) and additional risk minimisation measures (aRMMs) would not provide an added value given the specialist management, the population at risk and the nature of the illness.

The PRAC noted the systemic exposure is negligible following topical application of retinoids and that this does not appear to be affected to a clinically significant degree by the severity or extent of skin disease. Studies that examine the effects of human pregnancy on systemic absorption of topical retinoids are also lacking. However, there was a consensus that several other factors may contribute to an increased systemic exposure and therefore the risk cannot be excluded.

Given that humans are the most sensitive species with respect to retinoid toxicity and considering the limitations of the available data with respect to understanding the systemic absorption and also the possible risks, the PRAC, considers that it is appropriate to take a very precautionary approach. The indications for the topical retinoids are non-life-threatening and there is no absolute clinical need for the treatment during pregnancy and pregnancy should be excluded before prescribing. The PRAC thereby concludes that the benefit-risk balance of topical retinoids in pregnancy is not favourable, and therefore recommends that use of topical retinoids should be contraindicated during pregnancy and in women planning a pregnancy.

The PRAC recognizes that the available data in relation to oral retinoids and the occurrence of neuropsychiatric disorders have a number of important limitations that preclude the establishment of a clear causal association. Nevertheless, the PRAC considers that the data from patients presented in case series, spontaneous case reports and individual patients' experiences are considered to be very important. Although the underlying risk of psychiatric disorders within the patient populations can be significant, it is advisable that patients taking oral retinoids are warned about the potential risk of psychiatric reactions and the signs and symptoms to look out for. Therefore, the PRAC agrees that all oral retinoids should contain a warning about the potential risk of neuropsychiatric disorders in line with some key principles. The data support that for isotretinoin and alitretinoin the information in section 4.4 and 4.8, of the SmPC, should be in line with the agreed outcome of the 2003 Art 30 referral for isotretinoin.

The PRAC further noted the extremely limited data relating to neuropsychiatric reactions after topical administration of retinoids. Given this and the negligible systemic exposure following topical no further risk minimization activities are deemed necessary.

Overall, the PRAC concludes that the benefit-risk balance of medicinal products containing retinoids remains favourable, but that marketing authorisation(s) should be varied for both the oral and topical retinoids to ensure risks associated with the adverse teratogenic effects and neuropsychiatric disorders are accurately and consistently addressed, as appropriate.

### **Grounds for PRAC recommendation**

Whereas,

- The Pharmacovigilance Risk Assessment Committee (PRAC) considered the procedure under Article 31 of Directive 2001/83/EC for retinoid-containing medicinal products.
- The PRAC considered the totality of the data submitted, including responses from the marketing authorisation holders with regard to the consistency and effectiveness of existing routine and additional risk minimisation measures for oral and topical retinoids-containing medicinal products in relation to teratogenic effects and neuropsychiatric disorders. In addition, the PRAC considered the views of patients and healthcare professionals in relation to their understanding and the awareness of the teratogenic risk associated with the use of retinoid-containing medicines.
- With regards to the teratogenic risk, the PRAC confirmed that all oral retinoids (acitretin, alitretinoin, bexarotene, isotretinoin and tretinoin) are highly teratogenic and therefore must continue to be contraindicated during pregnancy or in women of child bearing potential unless they are using effective contraception. Given the indications and patients populations that use acitretin, alitretinoin and isotretinoin, it was considered that any use of these oral retinoids in female patients at risk of pregnancy must be in accordance with the conditions of a pregnancy prevention programme (PPP). For tretinoin and bexarotene, it was considered that in light of the oncological indications, specialist management in a hospital setting and population at risk that existing risk minimisation was appropriate and proportionate.
- The PRAC also concluded that there was a need to further harmonise and streamline the measures in the PPP including associated educational materials for the oral retinoids acitretin, alitretinoin and isotretinoin to ensure these are optimal to support discussions between patients and healthcare professionals on the risks and the associated risk minimisation measures.
- The PRAC further considered that for the oral retinoids acitretin, alitretinoin and isotretinoin a drug utilisation study with a complementary survey should be conducted to assess the effectiveness of the proposed updated risk minimisation measures.
- A direct healthcare professional communication (DHPC) was also considered appropriate for all oral and topical retinoids.
- With regards to the teratogenic risk of topical retinoids (adapalene, alitretinoin, isotretinoin, tretinoin and tazarotene), the PRAC concluded that the data available show that after topical application, systemic exposure is expected to be negligible and unlikely to result in adverse fetal outcomes. However, given that humans are the most sensitive species to retinoid embryopathy and that several other factors may contribute to an increased systemic exposure, such as excessive use and damaged skin barrier, the PRAC agreed that the teratogenic risk cannot be completely excluded. The PRAC therefore recommended that the use of topical retinoids should be contraindicated during pregnancy and in women planning a pregnancy given the non-life threatening nature of the indications.

- With regards to neuropsychiatric disorders, the PRAC noted the limitations of the available data and considered that a clear causal relationship could not be established with the oral retinoids. However, taking into account the target patient population, the PRAC recognised the possible underlying risk of psychiatric disorders, and therefore recommended some changes to the product information such as warnings and precautions and so that the current level of available evidence is appropriately reflected.
- Furthermore, the PRAC noted the extremely limited data relating to neuropsychiatric reactions after topical administration of retinoids. Given this and the negligible systemic exposure following topical use, the PRAC considered that no further risk minimization activities are deemed necessary.

In view of the above, the PRAC considers that the benefit-risk balance of retinoid-containing medicinal products remains favourable subject to the agreed amendments to the product information and risk management plan, the conditions to the marketing authorisations and the related communication.

The PRAC, as a consequence, recommends the variation to the terms of the marketing authorisations for retinoid-containing medicinal products.

### **CHMP opinion**

Having reviewed the PRAC recommendation, the CHMP agrees with the PRAC overall conclusions and grounds for recommendation.

The CHMP clarified that the communication plan should be modified to say ‘healthcare professionals who may be involved in the management of patients treated with retinoids’.

### ***Overall conclusion***

The CHMP, as a consequence, considers that the benefit-risk balance of retinoid-containing medicinal products remains favourable subject to the agreed amendments to the product information and risk management plan, the conditions to the marketing authorisations and the related communication.

Therefore the CHMP recommends the variation to the terms of the marketing authorisations for retinoid-containing medicinal products.